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(54) Title: PROCESS FOR THE PREPARATION OF 7-AMINO (p-HYDROXYPHENYLGLYCYL) CEPHEM COMPOUNDS

(57) Abstract: The invention relates to pure 7- amino (p-hydroxyphenylglycyl) cephem compounds. The invention also relates to processes for the preparation of pure 7- amino (p-hydroxyphenylglycyl) cephem compounds and pharmaceutical compositions that include the pure 7- amino (p-hydroxyphenylglycyl) cephem compounds.

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PROCESS FOR THE PREPARATION OF 7-AMINO (p-HYDROXYPHENYLGLYCYL) CEPHEM COMPOUNDS

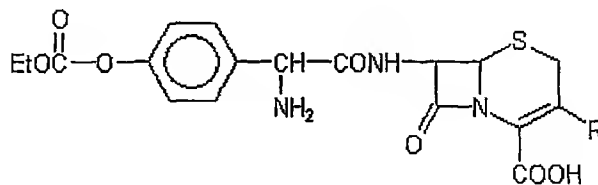
Field of the Invention

5 The field of the invention relates to pure 7- amino (p-hydroxyphenylglycyl) cephem compounds. The invention also relates to processes for the preparation of pure 7- amino (p-hydroxyphenylglycyl) cephem compounds and pharmaceutical compositions that include the pure 7- amino (p-hydroxyphenylglycyl) cephem compounds.

Background of the Invention

10 7- amino (p-hydroxyphenylglycyl) cephem compounds such as cefprozil, cefadroxil and cefatrizine are generally prepared by reacting a cephem derivative with a reactive derivative, such as a reactive ester; a reactive amide; and a mixed-acidic anhydride of 4-hydroxyphenylglycine.

15 British Patent GB 1,240,687 discloses a process involving reacting N-protected 4- hydroxyphenylglycine with ethyl chloroformate to obtain a carbonate derivative which is acylated with a cephem compound. However, this method gives a product of low purity. A major impurity formed in such a process has the structure of Formula A,



FORMULA A

20 wherein R is a group commonly used at the 3-position in cephalosporins, for example, methyl, 1-propenyl and 1,2,3-triazol-5-yl thiomethyl.

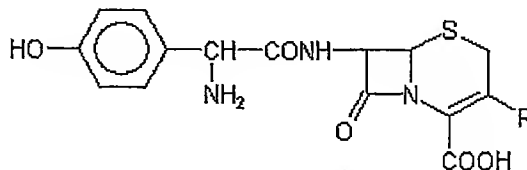
It was observed that this impurity is formed by reaction of ethyl chloroformate with the phenolic hydroxyl group under basic reaction conditions employed.

Thus, the present invention provides a process which results in pure 7- amino (p-hydroxyphenylglycyl) cephem compounds. The process of the present invention avoids

purification by tedious and cumbersome processes. The process of the present invention reduces the impurity content of the final product, eliminates the costly and time-consuming purification steps.

Summary of the Invention

5 In one general aspect there are provided pure cephem compounds of Formula I,



FORMULA I

wherein R is a group commonly used at the 3-position in cephalosporins and may include C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₂₋₆ alkadienyl, cyclic C₃₋₆ alkyl, aryl, substituted aryl, heteroaryl, or heteroarylthioalkyl. In particular, it may include methyl, 1-
10 propenyl and 1,2,3-triazol-5-yl thiomethyl.

In another general aspect there is provided a process for the preparation of cephem compounds of Formula I.

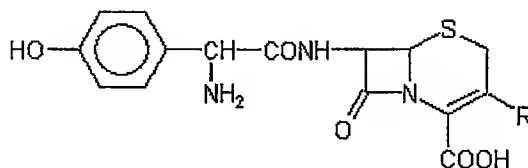
In another aspect there is provided a pharmaceutical composition and dosage forms containing a therapeutically effective amount of the cephem compounds of Formula I and
15 which may also contain pharmaceutically acceptable carriers, excipients or diluents which are useful for the treatment of bacterial infections.

In another aspect there is provided a method of treating bacterial infections comprising administering to a mammal in need thereof, a therapeutically effective amount of cephem compounds of Formula I as described above.

20 The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.

Detailed Description of the Invention

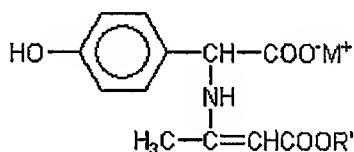
The inventors have developed a process for the preparation of certain cephem compounds of Formula I,



FORMULA I

- 5 wherein R is a group commonly used at the 3-position in cephalosporins and includes C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₂₋₆ alkadienyl, cyclic C₃₋₆ alkyl, aryl, substituted aryl, heteroaryl, or heteroarylthioalkyl. In particular, it includes methyl, 1-propenyl and 1,2,3-triazol-5-yl thiomethyl. The process comprising:

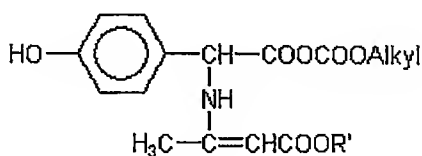
- (i) . . . reacting a Dane salt of Formula III,



FORMULA III

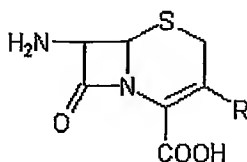
wherein R' is C₁₋₄ alkyl and M⁺ is an alkali metal cation,

with a lower alkyl chloroformate in the presence of an amine, and an acid, to obtain a mixed carboxylic acid anhydride of Formula IV, and



FORMULA IV

(ii) reacting the mixed carboxylic acid anhydride with a silylated derivative of the 7-amino-ceph-3-em-4-carboxylic acid of Formula II,

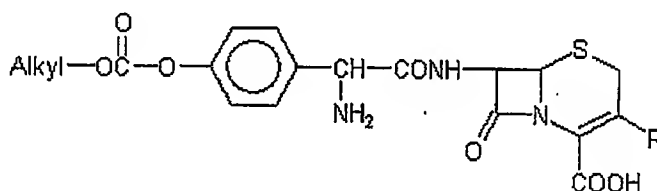


FORMULA II

wherein R is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₂₋₆ alkadienyl, cyclic C₃₋₆ alkyl, aryl,
5 substituted aryl, heteroaryl, or heteroarylthioalkyl,

to obtain the cephem compound of Formula I.

In general, the preparation of the mixed anhydride is carried out in the presence of a small amount of an acid to minimize the formation of impurity of Formula B, in the step ii) reaction,



FORMULA B

wherein R is a group commonly used at the 3-position in cephalosporins, and includes C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₂₋₆ alkadienyl, cyclic C₃₋₆ alkyl, aryl, substituted aryl, heteroaryl, or heteroarylthioalkyl.

The process is useful for the preparation of a wide variety of 7- amino(p-
15 hydroxyphenylglycyl) -cephalosporins, for example, cefatrizine, cefadroxil, or cefprozil, in good yield and purity.

Examples of Dane salts of Formula III include sodium or potassium D-N-(1-methoxycarbonylpropen-2-yl)amino-p-hydroxyphenyl- acetate, and sodium or potassium D-N-(1-ethoxycarbonyl- propen-2-yl)-amino-p-hydroxyphenylacetate.

Examples of alkyl chloroformates include ethyl chloroformate and methyl chloroformate.

Examples of amines present as a catalyst for mixed carboxylic acid anhydride formation include N-methyl morpholine, N,N-dimethyl benzyl amine, pyridine, picoline,
5 and lutidine.

The mixed anhydride may be prepared in one or more solvents, including, for example, halogenated hydrocarbon, ketone, ester, ether, nitrile, aromatic hydrocarbon, amide and mixtures thereof. Examples of chlorinated hydrocarbons include dichloromethane and dichloroethylene; Examples of ketones include acetone and methyl
10 isobutyl ketone; Examples of ester include ethyl acetate and isopropylacetate; Examples of ether include tetrahydrofuran and dioxane; a nitrile includes acetonitrile; Examples of aromatic hydrocarbon include toluene. A suitable co-solvent may be used with a solvent, for example amide. A suitable amide includes one or more of formamide, acetamide, N,N-dimethyl formamide, N-methylacetamide, N,N-dimethylacetamide and N-
15 methylpyrrolidone. Mixtures of all of these solvents are also contemplated.

The formation of the mixed carboxylic acid anhydride may be carried out at temperatures, from about -80°C to about 50°C, or from about -50°C to about 5°C.

The product of step i) is generally obtained as a solution or a suspension of the mixed carboxylic acid anhydride, and can be further used as such. If desired, this
20 anhydride may be maintained at from about -60°C to about -20°C.

The 7-amino-ceph-3-em-4-carboxylic acid of Formula II may be silylated with silylation agents in a solvent inert under the reaction conditions. Examples of silylation agents include mono- or bissilylated amides, such as N,O-bis-(trimethylsilyl)acetamide (BSA), N-methyl-N-trimethylsilyl-acetamide (MSA); silylated ureas, such as N,N'-bis-
25 (trimethylsilyl)-urea (BSU); or silazanes, such as 1,1,3,3,3-hexamethyldisilazane (HMDS), in combination with a halosilane such as trimethylchlorosilane, dimethyldichlorosilane, or an amine, such as triethylamine, tert.octylamine.

The solvents used for mixed anhydride preparation above may be used for silylation of the 7-amino-ceph-3-em-4-carboxylic acid, and also for the step ii) reaction.

The reaction temperatures for the step ii) may be from about -60°C to room temperature or from about -40 ° C to about -10°C.

The reaction mixture of the step ii) may be worked up in a conventional manner. The substituted vinyl group may be split by hydrolysis in aqueous acid.

5 The final product may be isolated in a conventional manner, for example by adjusting the pH of the reaction mixture. The product of Formula I can be obtained in a very high purity, for example above 98%.

 The 7-amino-ceph-3-em-4-carboxylic acid of Formula II may be prepared in accordance with any of the known methods (see U.S. Patent Nos. 3,867,380; 3 489,752
10 and 4,520,022).

 The Dane salt of Formula III may be obtained from commercial sources or prepared by methods well known in the art.

 Thus, compounds of Formula I having less than 0.5% by weight of the impurity of Formula B can be obtained. In particular, compounds of Formula I having less than 0.1%
15 by weight of the impurity of Formula B, or less than 0.05% can be obtained.

 The resulting cephem compounds of Formula I may be formulated into ordinary dosage forms such as, for example, tablets, capsules, pills, solutions, etc. In these cases, the medicaments can be prepared by conventional methods with conventional pharmaceutical excipients.

20 The compositions include dosage forms suitable for oral and parenteral (including subcutaneous, intramuscular, and ophthalmic) administration. The oral dosage forms may include solid dosage forms, like powder, tablets, capsules, as well as liquid suspensions. Parenteral dosage forms may include intravenous infusions, sterile solutions for intramuscular, subcutaneous or intravenous administration, dry powders to be
25 reconstituted with sterile water for parenteral administration, and the like.

 The present invention is further illustrated by the following examples which are provided merely to be exemplary of the invention and are not intended to limit the scope of the invention. Although the examples are directed to the cefprozil and cefdroxil, the principles described in these examples can be applied to other cephem compounds.

Example 1Cefprozil

7-amino-3-(propen-1-yl)-3-cephem-4-carboxylic acid (7-APCA, 50g) was added to methylene chloride (300ml). 1,1,3,3-hexamethylsilazane (25g), chlorotrimethylsilane
5 (17.5g) and imidazole (0.5g) were added. The reaction mixture was refluxed for 3-4 hours and then cooled to 0 to 5°C.

Potassium (D)-N-(1-methoxycarbonyl-propen-2-yl)- α -amino-p-hydroxyphenyl acetate (Dane salt, 71g) was added to methylene chloride (300ml) and dimethylformamide (200ml) and stirred at -40 to -45°C. N-methylmorpholine (0.42g) and methanesulfonic
10 acid (1.0 g) were added followed by ethylchloroformate (28.2g) and stirred for about 90 minutes at -35 to -40°C. It was then cooled to -65 to -70°C.

The suspension of silylated 7-APCA was added to the above mixed anhydride at -65 to -70°C and further stirred for 60 minutes at -40 to -45°C. The temperature was raised to -20 to -25°C and further stirred for 90 minutes. A mixture of water (170ml) and 35%
15 hydrochloric acid (35 ml) was added to the reaction mixture and stirred for 15 minutes at 0 to 5°C. The aqueous layer was diluted with dimethylformamide(700ml) and acetone (150 ml), and pH of the mixture adjusted to 6.5 with 25% ammonia solution. The mixture was stirred at 20-25°C for 2 hours and the separated solid was filtered. The solvate was washed dimethylformamide (100 ml) followed by acetone and dried at 40°C to yield 98g
20 of cefprozil as dimethyl formamide (1.5 mole) solvate.

Moisture content by KF = 0.25%; HPLC purity =99.58%; DMF content (by GC) = 18.2%

Impurity of formula B (R = 1-propenyl, Alkyl = ethyl) = 0.05% (by HPLC)

Above cefprozil dimethyl formamide solvate was converted to crystalline cefprozil
25 monohydrate by the procedure reported in U.S. Patent No. 4,694,079.

Example 2Cefadroxil

7-amino-3-desacetoxy-3-cephem-4-carboxylic acid (7-ADCA, 50g) was added to methylene chloride (300ml). 1,1,3,3-hexamethylsilazane (26g), chlorotrimethylsilane
5 (18.7g) and imidazole (0.5g) were added. The reaction mixture was refluxed for 3-4 hours and then cooled to 0 to 5°C.

Potassium (D)-N-(1-methoxycarbonyl-propen-2-yl)- α -amino-p-hydroxyphenyl acetate (Dane salt, 79g) was added to methylene chloride (300ml) and dimethylformamide (200ml) and stirred at -40 to -45°C. N-methylmorpholine (0.47g) and methanesulfonic
10 acid (1.12 g) were added followed by ethylchloroformate (29.5g) and stirred for about 90 minutes at -35 to -40°C. It was then cooled to -65 to -70°C.

The suspension of silylated 7-ADCA was added to the above mixed anhydride at -65 to -70°C and further stirred for 60 minutes at -40 to -45°C. The temperature was raised to -20 to -25°C and further stirred for 90 minutes. A mixture of water (170ml) and 35%
15 hydrochloric acid (35 ml) was added to the reaction mixture and stirred for 15 minutes at 0 to 5°C. The aqueous layer was diluted with dimethylformamide (700ml) and acetone (150 ml), and pH of the mixture adjusted to 6.5 with 25% ammonia solution. The mixture was stirred at 20-25°C for 2 hours and the separated solid was filtered. The solvate was washed dimethylformamide (100 ml) followed by acetone and dried at 40°C to yield 105g
20 of cefadroxil as dimethyl formamide (1.5 mole) solvate.

Moisture content by KF = 0.48%; HPLC purity = 99.24%; DMF content (by GC) = 22.8%

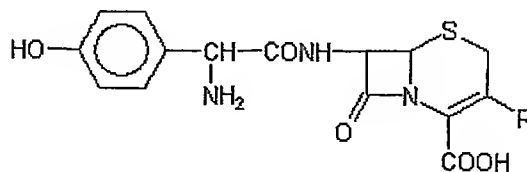
Impurity of formula B (R = methyl, Alkyl = ethyl) = 0.08% (by HPLC)

Above cefadroxil dimethyl formamide solvate was converted to white crystalline
25 solid cefadroxil monohydrate by the procedure reported in U.S. Patent No. 4,504,657.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

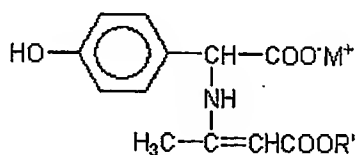
WE CLAIM:

1. A process for the production of a cephem compound of Formula I,

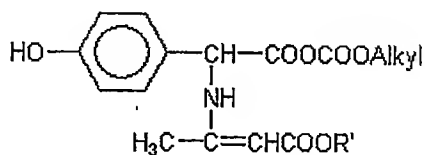
**FORMULA I**

- wherein R is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₂₋₆ alkadienyl, cyclic C₃₋₆ alkyl, aryl, substituted aryl, heteroaryl, or heteroarylthioalkyl, the process comprising:

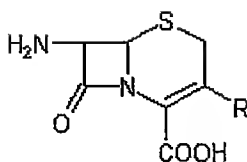
- i) reacting a Dane salt of Formula III,

**FORMULA III**

- wherein R' is C₁₋₄ alkyl and M⁺ is an alkali metal cation, with a lower alkyl chloroformate in the presence of an amine, and an acid, to obtain a mixed carboxylic acid anhydride of Formula IV,

**FORMULA IV**

- wherein R' is as defined above and alkyl is methyl or ethyl, and
- ii) reacting the mixed carboxylic acid anhydride with a silylated derivative of the 7-amino-ceph-3-em-4-carboxylic acid of Formula II,



15 **FORMULA II**

16 wherein R is as defined above,

17 to obtain the cephem compound of Formula I.

18 2. The process of claim 1, wherein the R group is methyl, 1-propenyl and 1,2,3-
2 triazol-5-yl thiomethyl.

1 3. The process of claim 1, wherein the Dane salt used in step i) is selected from the
2 group consisting of sodium or potassium D-N-(1-methoxycarbonylpropen-2-yl)amino-p-
3 hydroxyphenyl- acetate, and sodium or potassium D-N-(1-ethoxycarbonyl- propen-2-yl)-
4 amino-p-hydroxyphenylacetate.

5 1 4. The process of claim 1, wherein the alkyl chloroformates is ethyl chloroformate or
2 methyl chloroformate.

1 5. The process of claim 1, wherein the amine is selected from the group consisting of
2 N-methyl morpholine, N,N-dimethyl benzyl amine, pyridine, picoline, and lutidine.

1 6. The process of claim 1, wherein step i) is performed in a solvent.

1 7. The process of claim 6, wherein the solvent comprises one or more of a
2 halogenated hydrocarbon, ketone, ester, ether, nitrile, aromatic hydrocarbon or mixtures
3 thereof.

1 8. The process of claim 7, wherein the solvent is selected from the group consisting
2 of dichloromethane, dichloroethylene, acetone, methyl isobutyl ketone, ethyl acetate,
3 isopropylacetate, tetrahydrofuran, dioxane, acetonitrile and toluene.

1 9. The process of claim 1, wherein the step i) is carried out at temperature from about
2 -80°C to about 50°C.

1 10. The process of claim 9, wherein the step i) is carried out at temperature from about
2 -50°C to about 5°C.

1 11. The process of claim 6, wherein a co-solvent is used.

1 12. The process of claim 11, wherein the co-solvent is selected from the group
2 consisting of formamide, acetamide, N,N-dimethyl formamide, N-methylacetamide, N,N-
3 dimethylacetamide, and N-methylpyrrolidone.

1 13. The process of claim 1, wherein the step ii) is performed in a solvent.

1 14. The process of claim 13, wherein the solvent comprises one or more of
2 halogenated hydrocarbon, ketone, ester, ether, nitrile, aromatic hydrocarbon, or mixtures
3 thereof..

1 15. The process of claim 14, wherein the solvent is selected from the group consisting
2 of dichloromethane, dichloroethylene, acetone, methyl isobutyl ketone, ethyl acetate,
3 isopropylacetate, tetrahydrofuran, dioxane, acetonitrile and toluene.

1 16. The process of claim 1, wherein the step ii) is carried out at temperatures from
2 about -60°C to about 25°C.

1 17. The process of claim 16, wherein the step ii) is carried out at temperatures from
2 about -40°C to about -10°C.

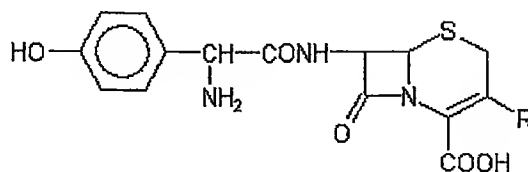
1 18. The process of claim 1, wherein the silylation of the 7-amino-ceph-3-em-4-
2 carboxylic acid of Formula II is carried out with a silylation agent selected from the group
3 consisting of mono- or bissilylated amides, silylated ureas, and silazanes, in combination
4 with a halosilane or an amine.

1 19. The process of claim 18, wherein the silylation agent is selected from the group
2 consisting of N,0-bis-(trimethylsilyl)acetamide (BSA), N-methyl-N-trimethylsilyl-
3 acetamide (MSA), N,N'-bis-(trimethylsilyl)-urea (BSU), and 1 1 3,3,3-
4 hexamethyldisilazane (HMDS),

1 20. The process of claim 18, wherein the halosilane is trimethylchlorosilane and
2 dimethyldichlorosilane.

1 21. The process of claim 18, wherein the amine comprises one or more of
2 triethylamine, and tert.octylamine.

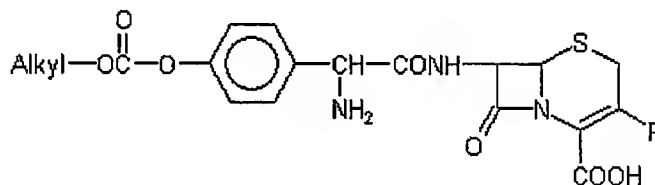
1 22. Compounds of Formula I,



2 **FORMULA I**

3 wherein R is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₂₋₆ alkadienyl, cyclic C₃₋₆ alkyl, aryl,
4 substituted aryl, heteroaryl, or heteroarylthioalkyl,, having less than 0.5% by weight of the
5 impurity of Formula B,

6



7 **FORMULA B**

8 wherein R is as defined above.

1 23. The compound of claim 22, wherein the R group is methyl, 1-propenyl and 1,2,3-
2 triazol-5-yl thiomethyl.

1 24. The compound of claim 22, wherein the impurity of Formula B is less than 0.1%
2 by weight.

1 25. The compound of claim 24, wherein the impurity of Formula B is less than 0.05%
2 by weight.

1 26. The compound of claim 22 or 23, wherein the alkyl group in the impurity of
2 Formula B is methyl or ethyl.

1 27. A pharmaceutical composition comprising the compound of claim 22 or 23
2 optionally together with pharmaceutically acceptable carriers, excipients or diluents.

1 28. A pharmaceutically acceptable composition comprising a pharmaceutically
2 acceptable effective amount of a compound according to claim 22 or 23 with a
3 pharmaceutically acceptable carrier for treating bacterial infections.